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PRINCIPAL INVESTIGATOR: Brian L. Pagenkopf, Ph.D.

CONTRACTING ORGANIZATION: University of Texas at Austin
Austin, Texas 78713-7726

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Brian L. Pagenkopf, Ph.D.

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

University of Texas at Austin
Austin, Texas 78713-7726

E-Mail: Pagenkopf@mail.utexas.edu

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13. Abstract ***(Maximum 200 Words)*** *(abstract should contain no proprietary or confidential information)*

Toward the objective of creating new acetogenin analogs as potential therapeutics for treating prostate cancer, all of the key substructures and building blocks have been prepared, and assembling them into the first analogs has commenced. All synthetic challenges encountered during the project thus far have been successfully overcome, and work is proceeding as planned. As an additional bonus from this work, a new cobalt complex was developed that catalyzes the stereoselective oxidative cyclization of bis-homoallylic alcohols to trans-tetrahydrofurans in high yield. This new catalyst is likely to see wide spread use in medicinal chemistry.

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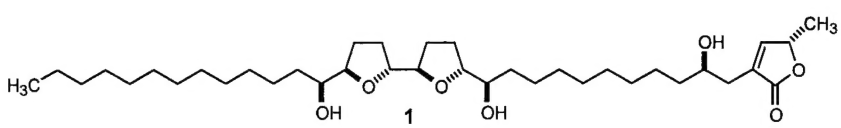
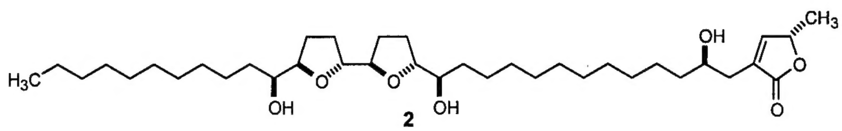
Table of Contents

INTRODUCTION

The objective of this work is to prepare synthetic analogs based on the natural acetogenins squamotacin **1** and bullatacin **2**, which show promising selective cytotoxicity toward prostate cancer cell lines, so that structure-activity relationships concerning the location of the bis-THF part of the molecule relative to the rest of the structure can be investigated.[1] We recently completed the synthesis of key building blocks and substructures necessary for analog production, and overcame some significant and unexpected synthetic complications regarding the preparation of the critical diol **3**.

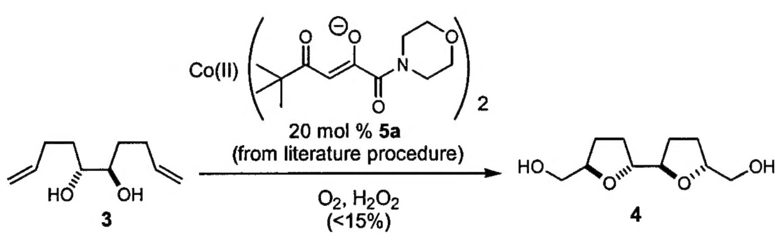




BODY

Part I of III. Preparation of all key starting materials. The first goal in the approved statement of work was to develop an efficient route to the central bis tetrahydrofuran core **4** that was capable of providing sufficient quantities for analog production, and this goal has been met. Our initial plan to prepare **4** was by the cyclization of the tartrate-derived diol **3** by cobalt catalyzed Mukaiyama oxidation.[2]

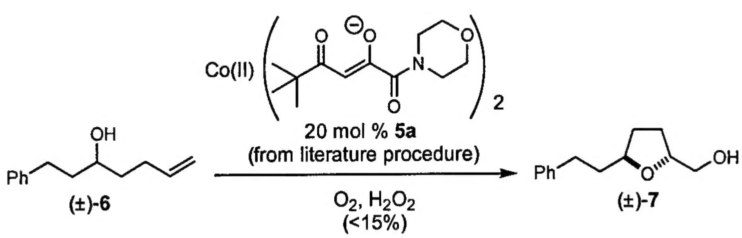
Scheme 1



The particular Mukaiyama oxidation identified for our use had seen little use in synthesis despite its promise to substantially simplify THF preparation. Since publication of the original paper in 1990,[2] it has been sited in total only 14 times by the groups of Shi,[3] Hartung,[4] Iqbal,[5] and Mukaiyama[6] (in a review). While other highly practical oxidations pioneered from the Mukaiyama laboratories have been widely adopted,[7,8] this catalytic oxidation appeared to be underutilized given the great need for efficient catalysts for THF syntheses. Our reason for selecting a somewhat speculative transformation in a key step was that the Chinese group of Wang, Shi, et al[3] had reported the use of the Mukaiyama catalyst for the synthesis of the bis-THF **4** with impressive efficiency. However, in our hands the prescribed conditions for the Co(modp)$_2$ catalyzed oxidation surprisingly only caused decomposition of **3**, and yields with the simpler model substrate **6** never surpassed ~15%

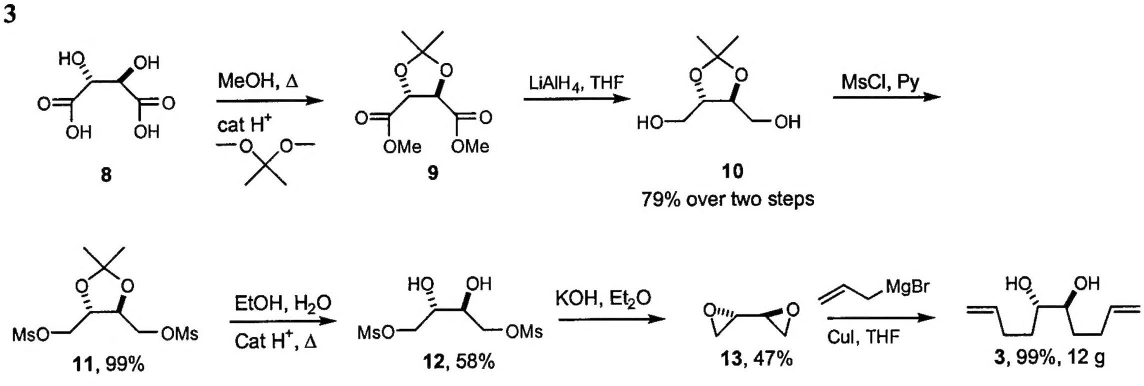
(Scheme 2). While we considered abandoning the original synthetic strategy for **3** and then employing a more laborious route, the synthetic potential of the elusive cobalt catalyzed THF synthesis and the prospect of developing an environmentally benign catalyst capable of generating biologically important tetrahydrofurans was sufficiently enticing that we decided to spend some time to investigate this reaction. *The bottom line is that as a direct result of our inquiry into this reaction the yield of THF **4** increased from an insignificant 15% to a preparatively useful 85% isolated yield, and similarly, the yield of the bis-THF **4** increased from 0% to 69%,* and these results are summarized in the next section. While catalyst development was not a part of the statement of work, these new catalysts are important new reagents that will have a major impact on stereoselective THF synthesis, which is important for medicinal chemistry and projects far beyond this one. We plan to submit two papers within the next several months on these new catalysts that will summarize our findings, but that work is not yet completed. Curiously, the Chinese group of Wang, Shi, et al continue to publish on this reaction without any of the sort of significant modifications to the original procedure that we determined are absolutely essential. Additionally, the NMR data reported by Wang, Shi, et al does not match ours or previously reported values, so their claims appear inaccurate.[3]

Scheme 2



The chiral diol **3** was prepared according to Scheme 3. We found that the efficiency of the $LiAlH_4$ reduction of **9** was greatly increased with a modification of the *Organic Syntheses* preparation that entailed simply switching the ether solvent for THF.[9] In the overall transformation, 100 g of tartaric acid **11** can be converted to diol **13** in >12% overall yield, and this route will be able to provide adequate quantities of material for the analog synthesis. We anticipate that now that some more details have been worked out the overall yield will approach 25%.

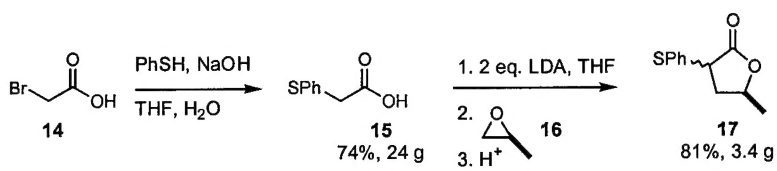
Scheme 3



While some of the long chain alkyl halides necessary for the analog synthesis are commercially available, those in the first series of analogs requiring synthesis were prepared by literature methods: 7-chloro-1-heptene, 8-chloro-1-octene and 9-chloro-1-nonene in 48% (1.6 g), 38% (1.2 g) and 66% (2.4 g) yield, respectively.[10] These syntheses worked well and we are confident they can be scaled up to supply more material as needed.

The precursor for the right hand butenolide portion for the acetogenin analogs was prepared as shown in Scheme 4. The propylene oxide **16** was resolved with Jacobsen catalyst,[11] and currently we have 17 g of the resolved epoxide in hand. The 2(phenylthio)acetic acid, obtained from thiophenol and bromo acetic acid,[12] was dilithiated with LDA and treated with the resolved propylene oxide **16**, which gave the lactone **17** after acidic workup. No detailed procedures were published for this lactone forming reaction, and developing conditions for an efficient synthesis required more time than anticipated.[13] However, the synthesis of this portion of the molecule is now well worked out.

Scheme 4



Part II of III. New Phosphonate Chemistry. Now that we just acquired all of the pieces necessary for the acetogenin synthesis, our work will focus on coupling them together to make squamostatin (to unambiguously confirm structure) and analogs. As described in the original application, a variable length "spacer" will be coupled to the right hand butenolide portion, and while we are working with established chemistry to accomplish the coupling, we considered that a phosphonate coupling reaction might further simplify this process. In this regard, we were fortunate to discover high selectivity in a rhodium catalyzed olefin hydrophosphorylation reaction, and these results were published in *Organic Letters*. A copy of the *Organic Letters* paper is included in the appendix. We have not yet determined if access to the pinacol phosphonates by hydrophosphorylation will streamline the analog synthesis, but it will certainly find other applications in synthetic organic chemistry.

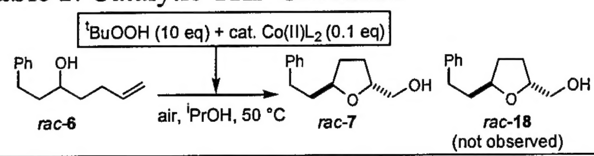
A copy of a second paper from *The Journal of Organic Chemistry* is included in the appendix, and it reports on the selective mono-desilylation of di-*tert*-butyl silylene ethers. While that paper is totally unrelated to the statement of work and was not supported by this Army medical research grant, the excitement from working on the acetogenin analog project has had a positive impact on other investigations underway in the laboratory. As the silylene work is likely to see use in medicinal chemistry, we felt that the Army funds helping to support our laboratory deserved acknowledgement.

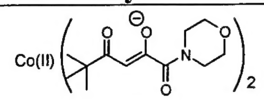
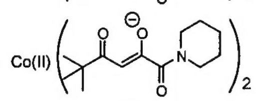
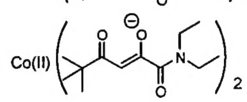
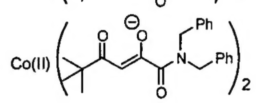
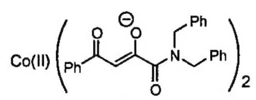
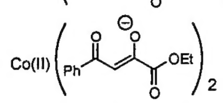
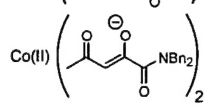
Part III of III. Details of the THF Synthesis. As mentioned in the previous section, we recognize that developing catalysts for stereoselective THF synthesis was not part of the original statement of work, but the new catalysts will keep the projected acetogenin analog project exactly on track as proposed. The key results of this THF work are presented here, and the final details, which are not yet available, will be provided in next year's report. Now that efficient routes to all the key acetogenin

building blocks have been prepared, we are focusing on analog production and polishing the final details to make the THF work ready for publication is not the current priority.

After some experimentation with the errant published procedures for the THF synthesis, it became clear the original oxidation protocol was fundamentally flawed. The new activity our catalysts in the oxidative cyclization required significant developments in three key areas, including new synthetic methods for synthesis of the ligands and devising a new H_2O_2 'activation' procedure. However, the critical breakthrough came from entirely new catalysts, and oxidation results are summarized in Table 1. Replacing the original morpholine amide with piperidine lead to a clear improvement in catalyst stability and THF yield (entry 2). The diethyl amide (entry 3) performed similarly, and blocking the beta hydrogens (entry 4) lead to another marked increase in catalyst stability resulting in an 85% isolated yield of **7** from the oxidation reaction. Remarkably, an unprecedented 84% yield was obtained with only 3 mol % of catalyst (entry 5). More severe changes to ligand structure have thus far attenuated catalyst activity. Replacing the amide with an ester greatly deteriorated the stability of the oxidized cobalt complex (entry 7).[14] In contrast, replacing the C(5) *tert*-butyl with a phenyl group made little difference in this reaction (entry 6), but the complex failed to catalyze the oxidation of diol **6**. Replacing the *tert*-butyl group with a methyl provided less favorable results. (entry 8). Interestingly, as a catalyst $Co(acac)_2$ was comparable to $Co(II)(modp)_2$ despite reports to the contrary (entry 9)[2] and $Co(III)(acac)_3$ showed no catalytic activity under these conditions (entry 10). In no instance was the diastereomeric syn-furan **18** detected, which was consistent with the original Mukaiyama report.[2]

Table 1. Catalytic THF Oxidation

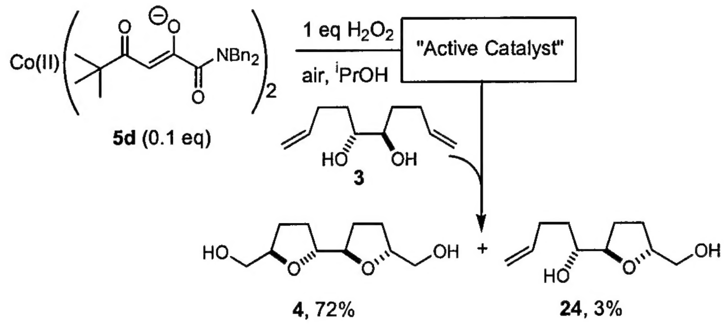


Entry	Precatalyst[a]	#	Yield[b]
1		**5a**	41%
2		**5b**	58%
3		**5c**	58%
4		**5d**	85%
5	3 mol % "	"	84%
6		**19**	63%
7		**20**	5%
8		**21**	43%
9	$Co(acac)_2$	**22**	41%
10	$Co(acac)_3$	**23**	No reaction[c]

[a] The precatalyst (10 mol %, unless otherwise noted) was activated with 10 eq of *t*BuOOH per cobalt prior to olefin addition. [b] Isolated yields, average of two runs or more, yields within 3% of average. [c] With or without hydroperoxide activation.

The dramatic improvements in the oxidative cyclization were made possible because of our new catalysts and procedures. The impressive performance displayed by complex **5d** successfully transferred to the oxidative cyclization diol **3**, and the bis-THF **4** can be reliably prepared in near 70% isolated yield. The new catalytic oxidations presented here will likely find widespread use and application in other areas of medicinal chemistry.

Scheme 5



Hundreds of tetrahydrofuran (THF) containing natural products have been isolated from marine and terrestrial sources, and some of these compounds, especially the polyether oligio-THF ionophores, display important biological properties such as exceptional Na^+, K^+ and Ca^{2+} ion transporting ability, selective cytotoxicity and significant antibiotic activity.[15] The frequent occurrence of the substituted THF substructure in biologically important compounds has revealed a need for succinct, stereoselective and efficient methods for their preparation, yet no catalytic methods for preparing the acetogenin stereochemical motif previously existed. These new catalysts are likely to find important application in future synthetic efforts.

KEY RESEARCH ACCOMPLISHMENTS

- Successfully completed a practical synthesis of the key bis-tetrahydrofuran core
- Developed a new and general catalyst for the synthesis of tetrahydrofurans
- Prepared all acetogenin substructures necessary for advancing the project

REPORTABLE OUTCOMES

Manuscripts

The Regioselective Mono-deprotection of 1,3-Dioxa-2,2-(di-*tert*-butyl)-2-silacyclohexanes with $BF_3{\bullet}SMe_2$. Ming Yu and Brian L. Pagenkopf, *J. Org. Chem.* **2002**, 67, 4553-4558.

Rhodium Catalyzed Regioselective Olefin Hydrophosphorylation. John F. Reichwein, Mittun C. Patel and Brian L. Pagenkopf, *Org. Lett.* **2001**, *3*, 4303-4306.

Presentations

November 16, 2001, "Catalytic Olefin Hydrophosphorylation and Horner-Like Coupling Reactions of Non-Stabilized Beta-Hydroxy Phosphonates." Brian L. Pagenkopf, University of Texas, Department of Chemistry; Arlington, Texas.

October 19, 2001, "Catalytic Olefin Hydrophosphorylation and Horner-Like Coupling Reactions of Non-Stabilized Beta-Hydroxy Phosphonates." Brian L. Pagenkopf, Southwest Regional ACS Meeting; San Antonio, Texas.

Funding Applied For

Support to develop the stereoselective THF synthesis has been requested from the National Institutes of Health. "Stereoselective Methods for Natural Product Synthesis," $750,000 Direct Costs.

Degrees Obtained

Mr. Mittun Patel completed is B.S. in biology while working on this project.

CONCLUSIONS

In the first year of this project we have fallen behind by a few months from the anticipated timeline, but the proposed timeline was based on a larger budget. We have successfully overcome unexpected complications in the synthesis of the bis-tetrahydrofuran starting material, and all of the remaining subsections or pieces of the proposed acetogenins have now been prepared. More importantly, every objective and task necessary to proceed with the proposed analog series is in place and the project goals are being met as intended. With all of the pieces or building blocks now in hand, their assembly into the proposed analogs can commence.

Additionally, an important new cobalt catalyzed stereoselective tetrahydrofuran synthesis has been discovered as a direct result of working on this acetogenin project, and this method constitutes the first transition metal catalyzed variant of this reaction. The ability to prepare stereochemically complex tetrahydrofurans in a single catalytic step under environmentally green and benign reaction conditions is a significant achievement, and one that will see application in a variety of medicinal chemistry applications.

Well, so what? The most important upcoming information we anticipate from this work will be on acetogenin biological activity, but this activity data will not be available until the new synthetic analogs are prepared (sometime next year). Everything is proceeding as planned to complete the important acetogenin syntheses. Furthermore, new olefin hydrophosphorylation and oxidative cyclization reactions have been discovered as a direct result of this work, and these high impact reactions will contribute substantially to synthetic and medicinal chemistry far beyond the objectives of this project.

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ORGANIC LETTERS

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Rhodium-Catalyzed Regioselective Olefin Hydrophosphorylation

John F. Reichwein, Mittun C. Patel, and Brian L. Pagenkopf*

Department of Chemistry and Biochemistry, The University of Texas at Austin, Austin, Texas 78712

pagenkopf@mail.utexas.edu

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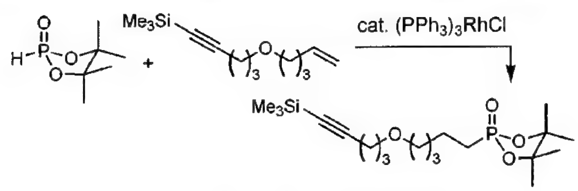
ABSTRACT



Parameters influencing the selectivity of the $(PPh_3)_3RhCl$-catalyzed hydrophosphorylation of olefins and enynes are described. The reaction between differentiated dienes was shown to be highly responsive to olefin substitution. The trimethylsilyl group effectively reversed the normal preference for hydrophosphorylation of an alkyne over an alkene.

New methods for phosphonate synthesis continue to attract attention because phosphonates display biologically important properties as natural products,[1] analogues of phosphates[2] (including RNA/DNA),[3] phosphonopeptides,[4] amino acid analogues,[5] and pro-drugs.[6] The number of methods for the preparation of organophosphonates is limited, and traditionally phosphonates are prepared by Arbuzov reaction of phosphites with organic halides.[7] Given the indispensable utility of phosphonates as bioactive molecules and synthetic tools (e.g., Wadsworth−Emmons and related reactions), research into the synthesis of phosphonates and associated reactions is important. In this regard, Tanaka recently reported the palladium(II)-catalyzed hydrophosphorylation of terminal and strained cyclic olefins with the pinacol-derived phosphonite **1** (Scheme 1).[8−0]

A significant advantage of transition metal catalyzed olefin hydrophosphorylations over traditional phosphonate synthesis is the mild reaction conditions. However, to successfully predict the effectiveness of the reaction in the context of a complex synthetic target with multiple sites of unsaturation, information regarding the selectivity of the olefin hydrophosphorylation is required. In addition to defining the parameters that influence the selectivity between differentiated olefins, the effect and compatibility with other functionalities such as amides and vinyl ethers need to be addressed. Currently, the major drawback of the hydrophosphorylation reaction shown in Scheme 1 is its dependence upon *cis*-$PdMe_2(PPh_2(CH_2)_4PPh_2)$ as catalyst, which is air-

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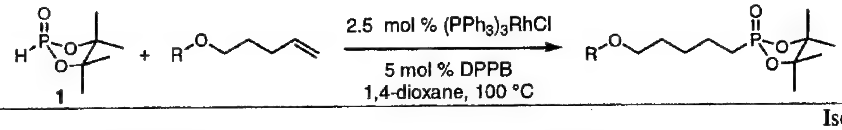
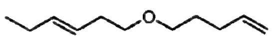
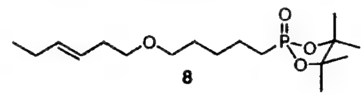
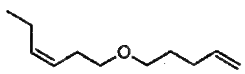
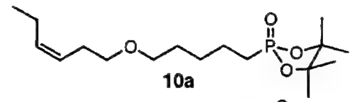
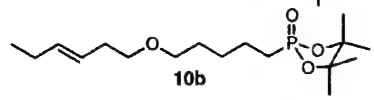
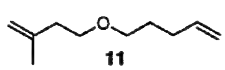
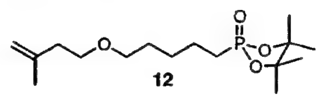
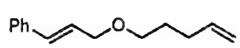
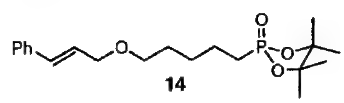
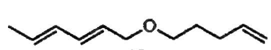
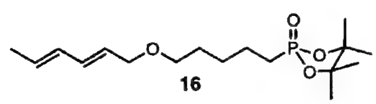
(6) For a review, see: Krise, J. P.; Stella, V. J. *Adv. Drug Delivery Rev.* **1996**, *19*, 287−310.
(7) (a) *Organic Phosphorus Compounds*; Kosolapoff, G. M., Maier, L., Eds.; Wiley-Interscience: New York, 1972. (b) *Handbook of Organophosphorus Chemistry*; Engel, R., Ed.; Marcel Dekker: New York, 1992. (c) Corbridge, D. E. C. *Phosphorus: An Outline of Its Chemistry, Biochemistry and Uses*, 5th ed.; Elsevier: Amsterdam, 1995.
(8) Han, L.-B.; Mirzaei, F.; Zhao, C.-Q.; Tanaka, M. *J. Am. Chem. Soc.* **2000**, *122*, 5407−5408.
(9) Radical olefin hydrophosphorylation is known: Stiles, A. R.; Vaughan, W. E.; Rust, F. F. *J. Am. Chem. Soc.* **1958**, *80*, 714−716.
(10) Alkyne hydrophosphorylation was reported previously, see: (a) Han, L.-B.; Zhao, C.-Q.; Tanaka, M. *J. Org. Chem.* **2001**, *66*, 5929−5932. (b) Han, L.-B.; Hua, R.; Tanaka, M. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 94−96. (c) Han, L.-B.; Choi, N. R.; Tanaka, M. *Organometallics* **1996**, *15*, 3259−3261. (d) Zhao, C.-Q.; Han, L.-B.; Goto, M.; Tanaka, M. *Angew. Chem., Int. Ed.* **2001**, *40*, 1929−1932.

10.1021/ol016989r CCC: $20.00
Published on Web 12/05/2001

Table 2. Selective Hydrophosphorylation

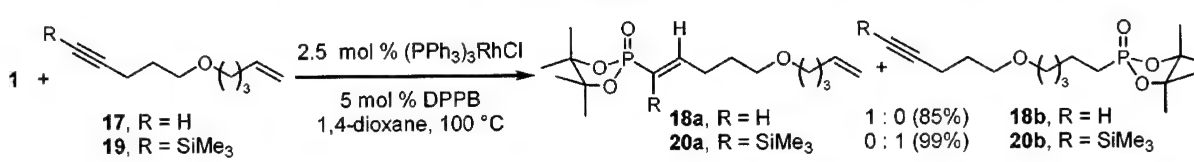


Entry	Substrate	Product(s)	Isolated Yield (ratio)
1	 7	 8	91%
2	 9	 10a  10b	81% (1:1)
3	 11	 12	95%
4	 13	 14	90%
5	 15	 16	56%

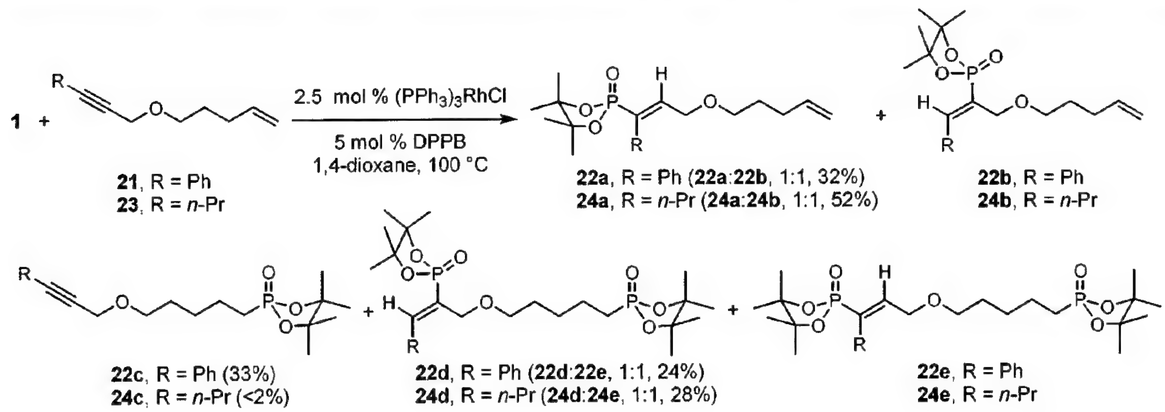
stereochemical scrambling to the trans olefin **10b** occurred in half of the product. Isomerization of the cis olefin suggests a close interaction with the rhodium catalyst, but no internal hydrophosphorylation was detected. In entry 3, preference for the terminal olefin over the 2,2-disubstituted alkene was observed. Attempts to achieve hydrophosphorylation at the remaining site of unsaturation in **12** by employing an excess of hydrogen phosphonate **1** were unsuccessful. In entry 4, the internal olefin is in conjugation with a phenyl ring, and this had no impact on the selectivity or yield of the reaction. In entry 5, only hydrophosphorylation was observed at the terminal olefin, and the low 56% yield was accredited to the instability of the product that decomposed on standing.[18]

While alkyne hydrophosphorylation is well documented,[10] no reports have appeared on the selectivity of hydrophosphorylation of alkynes versus monosubstituted olefins. To address this deficiency, treatment of enyne **17** under the standard reaction conditions[16] gave the *E* vinyl phosphonate **18a** as a single regio- and stereoisomer from hydrophosphorylation exclusively at the triple bond (Scheme 3). Importantly, substitution of the terminal alkyne with a trimethylsilyl protecting group (*n*-BuLi, THF, −78 °C; Me_3SiCl, 96%) resulted in a reversal of reactivity and only the olefin underwent hydrophosphorylation (**19** → **20b**). The TMS protecting group allows access to the terminal alkyne for further functionalization, as it can be easily removed with methanolic K_2CO_3 or Bu_4NF. In contrast to the impressive regioselectivity observed in the above experiments, competitive hydrophosphorylation with enynes **21** and **23** gave complex mixtures of regio- and stereoisomers (Scheme 4).

Scheme 3



Scheme 4



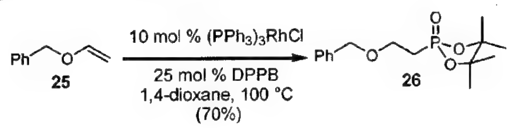
In summary, we have reported that $(PPh_3)_3RhCl$ in the presence of DPPB is an efficient catalyst for the hydrophosphorylation of olefins.[19] The reaction is highly sensitive to olefin substitution, and monosubstituted olefins can be reliably converted to their aliphatic phosphonates in the presence of other olefins. Additionally, a trimethylsilyl group is an effective acetylene protecting functionality that reverses the normal preference for alkyne hydrophosphorylation over a terminal olefin.

Acknowledgment. We thank the Robert A. Welch Foundation and the DOD Prostate Cancer Research Program DAMD17-01-1-0109 for financial support of our work. M.C.P. thanks the University of Texas at Austin for an undergraduate research fellowship.

Supporting Information Available: Spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL016989R

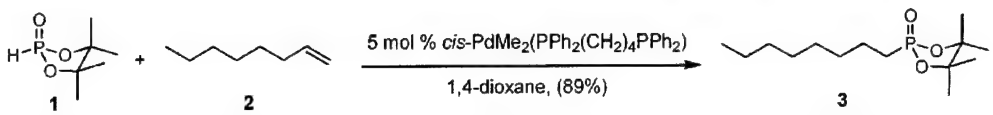
(17) To explore whether more significant electronic effects would influence the hydrophosphorylation of a monosubstituted olefin, the vinyl ether **25**, a substrate that offers an attractive synthetic handle for further synthetic modifications, was exposed to our standard reaction conditions.[16] This gave rather disappointing results, but by increasing both the catalyst loading and the reaction time (2 d) a 70% yield of the β-benzyloxy phosphonate **26** was obtained.



(18) Palladium-catalyzed hydrophosphorylation of dienes has been reported: Miraei, F.; Han, L.-B.; Tanaka, M. *Tetrahedron Lett.* **2001**, *42*, 297–299.

(19) The use of pinacol-derived phosphonates in Horner-like coupling reactions will be described elsewhere.

Scheme 1



sensitive and not commercially available.[11] A better catalyst would be commercially available, more robust and relatively air-stable. In this communication we disclose that Wilkinson's catalyst, $(PPh_3)_3RhCl$, efficiently catalyzes olefin hydrophosphorylation and describe the effect of alkene and alkyne substitution on the selectivity of the reaction.

A preliminary screening of various metal species in dioxane at 100 °C, including $Pd(PPh_3)_4$, $Pd_2(dba)_3$, and $(PPh_3)_3RhCl$, revealed that each catalyzed the hydrophosphorylation of 1-octene **2** in the presence of hydrogen phosphite **1**,[12] albeit in moderate yields (Table 1).[13] However,

Table 1. Effect of Metal Catalyst and Additives on the Hydrophosphorylation Reaction **1** + **2** → **3**[a]

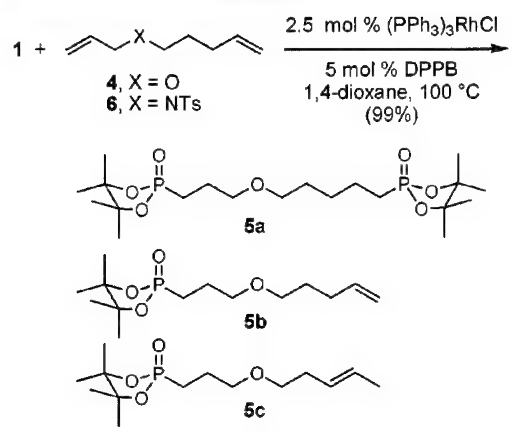
entry	catalyst	mol %	additive	yield[d] (%)
1[b]	$(PPh_3)_3RhCl$	5		57
2[c]	$(PPh_3)_3RhCl$	5	5% DPPB	95
3[c]	$(PPh_3)_3RhCl$	2.5	2.5% DPPB	91
4[b]	$(PPh_3)_3RhCl$	1.25	1.25% DPPB	85 (99)[e]
5[c]	$(PPh_3)_3RhCl$	1.25	5% DPPB	99
6[b]	$(PPh_3)_3RhCl$	5	10% Ph_3P	42
7[b]	$(PPh_3)_3RhCl$	5	10% $^nBu_3P$	nr[f]
8[b]	$(PPh_3)_3RhCl$	5	5% DPPB, 150% DMF	96
9[b]	$Pd(PPh_3)_4$	5		37
10[b]	$Pd_2(dba)_3$	2.5	5% DPPB	25

[a] Reactions were performed at 100 °C in 1,4-dioxane under an atmosphere of Ar. [b] One milimole scale. [c] Ten milimole scale. [d] Isolated yields. [e] After additional DPPB.[15] [f] No reaction.

in the presence of $Ph_2P(CH_2)_4PPh_2$ (DPPB), Wilkinson's catalyst gave excellent yields (entry 2, 95%).[14] The formation of DPPB oxides during the course of the reaction suggested that DPPB might serve to reduce a catalytically inactive oxidized rhodium species. In entry 4 the reaction failed to go to completion, but the stalled reaction resumed upon addition of additional DPPB.[15] In this regard, the addition of more than 1 equiv of DPPB per rhodium allowed efficient and reproducible hydrophosphorylation with low catalyst loading (1.25 mol % rhodium, entry 5). Substituting DPPB with more economical phosphines either had no effect on turnover versus Wilkinson's catalyst alone (Ph_3P, entry 6) or fully attenuated catalyst activity ($^nBu_3P$, entry 7).

With an active and convenient rhodium catalyst in hand, an investigation into its ability to differentiate between two dissimilar olefins was initiated. To determine whether subtle electronic effects could direct the hydrophosphorylation, diene **4** was treated with 0.9 equiv of **1** under the new catalysis conditions (Scheme 2).[16] The products **5a**, **5b**, and

Scheme 2



5c were obtained in a 1.3:1:1 ratio, and therefore only a small 3:1 preference existed for reaction at the allylic position. Additionally, isomerization of the bis-homoallylic olefin to an internal position occurred in **5c**. Similar yield and product distributions were observed with tosamide **6**.

While substrates **4** and **6** showed that a subtle electronic difference between olefins was insufficient to significantly control the regioselectivity of the hydrophosphorylation,[17] the catalyst was adept at distinguishing between disubstituted and monosubstituted olefins, as summarized in Table 2. In the competition between a terminal olefin and a stereochemically pure trans olefin (entry 1), reaction occurred only at the sterically more accessible position, and the stereochemical integrity of the trans olefin remained intact. In entry 2 complete regiocontrol was also observed, but in this instance

(11) de Graaf, W.; Boersma, J.; Smeets, W. J. J.; Spek, A. L.; van Koten, G. *Organometallics* **1989**, *8*, 2907–2917.

(12) The use of $HP(O)Ph_2$ and $HP(O)(OEt)_2$ failed in the reaction. Details will be described elsewhere.

(13) Similar results have been observed; see ref 8.

(14) Although reactions were typically assembled in an inert atmosphere glovebox, the use of Wilkinson's catalyst that had been stored exposed to air for weeks performed equally well provided 2 equiv of DPPB per Rh was added to the reaction.

(15) The reaction mixture was yellow throughout the initial period of the reaction but turned orange/brown before complete consumption of phosphonate **1** (85% yield from one-half of the reaction). After 2 mol % additional DPPB was added to the reaction, the yellow color returned and the reaction proceeded to completion.

(16) **General Experimental Procedure.** A round-bottomed flask was charged with the olefin (1.1 equiv), hydrogen phosphonate **1** (1.0 equiv), 2.5 mol % $(PPh_3)_3RhCl$, 5 mol % DPPB, and dioxane (0.25 M). The reaction mixture was heated at 100 °C for 20 h and then concentrated in vacuo. The phosphonates were purified by flash chromatography on silica gel.

J. Org. Chem. **2002**, *67*, 4553–4558

The Regioselective Mono-deprotection of 1,3-Dioxa-2,2-(di-*tert*-butyl)-2-silacyclohexanes with $BF_3 \cdot SMe_2$

Ming Yu and Brian L. Pagenkopf*

Department of Chemistry and Biochemistry, The University of Texas at Austin, Austin, Texas 78712

pagenkopf@mail.utexas.edu

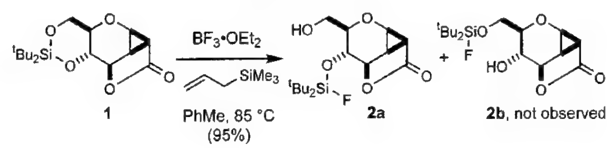
Received February 18, 2002

The selective mono-deprotection of di-*tert*-butylsilylene ethers prepared from substituted 1,3-pentanediols and 2,4-hexanediols has been achieved with $BF_3 \cdot SMe_2$. The reaction conditions are compatible with esters, allyl ethers, and TIPS ethers. The resulting di-*tert*-butylfluorosilyl ethers are stable to various conditions including low pH aqueous solutions and silica gel chromatography; the di-*tert*-butylfluorosilyl ethers are readily cleaved with HF–pyridine. Substrate stereochemistry and conformation influences the efficiency of the deprotection, while the deprotection regiochemistry is consistent with coordination of boron to the sterically more accessible oxygen prior to intramolecular delivery of fluoride.

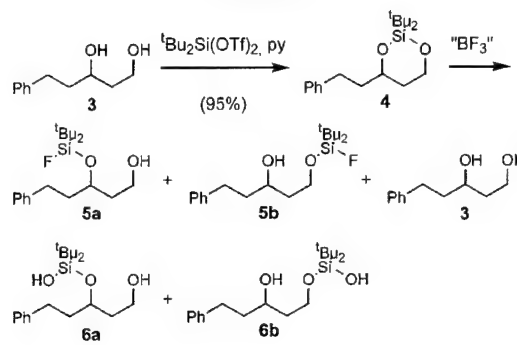
Introduction

The installation of protecting groups at the more hindered hydroxyl of 1,3-diols is frequently required in organic synthesis, but is not generally available by direct methods.[1] The task is often accomplished through multistep transformations, as with the hydridic cleavage of benzylidene acetals. Silylation at the more hindered site of a 1,3-diol is likewise complicated because standard conditions result in preferential reaction at the less hindered hydroxyl group.[2] The increased reactivity at the more accessible position normally permits selective deprotection at the less hindered site of a persilylated substrate.[3] A few reports have appeared regarding the ring opening of di-*tert*-butyl-, dicyclohexyl-, and diphenylsilylene ethers of 1,3- and 1,2-diols with Grignard or alkyllithium reagents.[4,5] Additionally, haloboranes are known to deprotect silyl ethers,[6,7] and have been used for the regioselective desilylation of *tert*-butyldimethylsilyl ethers.[8] We recently reported the highly regioselective mono-deprotection of the di-*tert*-butylsilylene ether **1** with $BF_3 \cdot OEt_2$ (85 °C, toluene), which gave exclusively the di-*tert*-butylfluoro silyl ether **2a** (Scheme 1).[9] In this Paper we illuminate some of the structural and chemical parameters that influence the mono-deprotection of ${}^tBu_2Si(OR)_2$ ethers, describe the reactivity of the $(F){}^tBu_2Si$ hydroxyl protecting group, and explore the compatibility of the method with other functionality.

Scheme 1



Scheme 2



Results and Discussion

The di-*tert*-butylsilylene ether **4**,[10] which like **1** was prepared from a primary and a secondary 1,3-diol, was selected as a model substrate to explore the generality of the $BF_3 \cdot OEt_2$-mediated deprotection (Scheme 2). Using conditions similar to those utilized for **1**,[11] the reaction with **4** provided the desired fluorosilane **5a** along with a

(1) (a) Green, W. P.; Wuts, P. G. M.; *Protective Groups in Organic Synthesis*; Wiley: Toronto, 1999. (b) Kociensky, P. J. *Protecting Groups*; Thieme: Stuttgart, 1994.

(2) Chaudhary, S. K.; Hernandez, O. *Tetrahedron Lett.* **1979**, *20*, 99–102.

(3) (a) Boschelli, D.; Takemasa, Y.; Nishitani, Y.; Masamune, S. *Tetrahedron Lett.* **1985**, *26*, 5239–5244. (b) Crimmins, M. T.; Lever, J. G. *Tetrahedron Lett.* **1986**, *27*, 291–294.

(4) The 1,1,3,3-tetraisopropyldisiloxane-1,3-diyl protecting group can be regioselectively mono-deprotected at the less hindered site: (a) Zhu, X. F.; Williams, H. J.; Scott, A. I. *Tetrahedron Lett.* **2000**, *41*, 9541–9545. (b) Pankiewicz, K. W.; Watanabe, K. A.; Takayanagi, H.; Itoh, T.; Ogura, H. *J. Het. Chem.* **1985**, *22*, 1703–1710.

(5) Tanino, K.; Shimizu, T.; Kuwahara, M.; Kuwajima, I. *J. Org. Chem.* **1998**, *63*, 2422–2423.

(6) Corey, E. J.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190–6191.

(7) Kelly, D. R.; Roberts, S. M.; Newton, R. F. *Synth. Commun.* **1979**, *9*, 295–299.

(8) Yang, Y.-Y.; Yang, W.,-B.; Teo, C.-F.; Lin, C.-H. *Synlett* **2000**, 1634–1636.

(9) Yu, M.; Lynch, V.; Pagenkopf, B. L. *Org. Lett.* **2001**, *3*, 2563–2566.

(10) Corey, E. J.; Hopkins, P. B. *Tetrahedron Lett.* **1982**, *23*, 4871–4874.

(11) The addition of allyl trimethylsilane to the reaction minimizes the formation of side products during the first few seconds after the addition of BF_3 and is presumably serving as a kinetically fast trap for HF.

10.1021/jo025624x CCC: $22.00
Published on Web 05/11/2002

Scheme 3

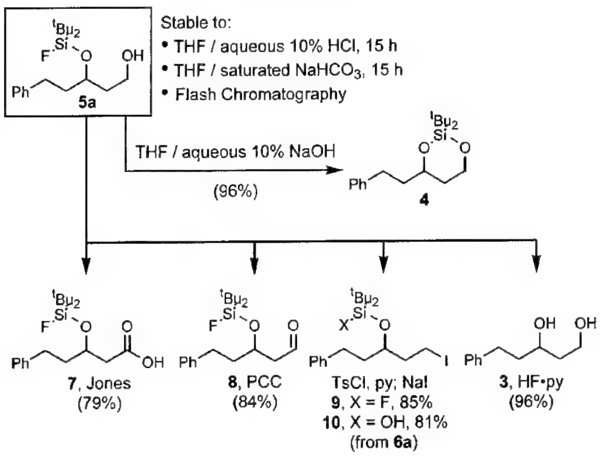
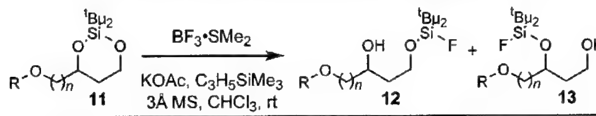


Table 1. Deprotection of Di-*tert*-butylsilylene Ethers in the Presence of Other Functionality



entry	*n*	R	product	yield, %[a]
a	2	H	-	decomp
b	1	CH_3CO	**13b**	91[b]
c	2	CH_3CO	**13c**	87
d	1	PhCO	**13d**	90
e	2	PhCO	**13e**	82
f	2	Allyl	**13f**	78[c]
g	2	$PhCH_2$	**11g**, **13g**	57, 35
h	2	CH_3	**11a**, **13h**	50, 43
i	2	$(i\text{Pr})_3Si$	**13i**	78%
j	2	$(t\text{Bu})Me_2Si$	**11a**	97%

[a] Isolated yields. [b] 8% of the isomeric fluorosilane **12b** was detected in the crude ^{19}F NMR. [c] 4% of **12f**.

disappointing mixture of its regioisomer **5b**, silanols **6a** and **6b**, diol **3**, and unreacted starting material. The addition of 3 Å molecular sieves to the reaction prevented the formation of silanols **6a** and **6b**, which were likely due to interaction with adventitious water. The screening of other commercially available BF_3–Lewis base complexes, including BF_3·THF, BF_3·ᵗBuOMe, and BF_3·MeOH, revealed that BF_3·SMe_2 improved both the conversion and selectivity of the reaction. However, the formation of considerable amounts of diol **3** continued to plague the process. The varying reactivity displayed by different BF_3 sources clearly demonstrated the importance of Lewis bases in the reaction, and a survey of assorted adjuncts including esters, ethers, amines, and salts showed that the addition of excess anhydrous potassium acetate to the reaction greatly minimized complete desilylation to diol **3**.[12] Replacing the toluene solvent with chloroform or hexane further minimized formation of diol **3**. With these modifications, the regioselective deprotection of **4** with BF_3·SMe_2 consistently gave the fluorosilanes **5a**:**5b** in a >15:1 ratio and 79–85% isolated yields.[13]

Although the selective deprotection of **4** under optimized conditions was promising, for this new transformation to be of value the fluorosilane products must be sufficiently robust to serve as viable protecting groups in subsequent reactions. In this regard, the fluorosilane **2a** survived several synthetic steps and flash chromatography.[9] Likewise, the fluorosilane **5a** was stable to aqueous acid for 15 h (THF, 10% aqueous HCl) and neutral solutions (THF, saturated $NaHCO_3$) (Scheme 3); however, more strongly basic conditions resulted in closure to the silylene ether **4** (THF, 10% aqueous NaOH, 15 min, 96%). Several transformations at the primary alcohol of the fluorosilane **5a** illustrate the stability of the (F)ᵗBu_2Si group, including Jones oxidation, PCC oxidation, and Finkelstein reaction. The silanol **6a** was also fairly stable, as demonstrated by its conversion to **10** in 81% yield. The di-*tert*-butylfluoro silane **5a** can be easily cleaved to the diol **3** with HF·pyridine (**5a** → **3**, 96%).[14]

With the integrity of the di-*tert*-butylfluorosilane ether amply demonstrated, substrate compatibility and availability of orthogonal protective functions was briefly surveyed. As anticipated, the Lewis acidic nature of the reaction media precluded the use of substrates with Lewis acid sensitive functionality. For example, at its current state of development, silylene ethers prepared from tertiary or benzylic alcohols predominately undergo elimination under the deprotection reaction conditions. The model substrates **11a–j** shown in Table 1 were used to explore the functional group orthogonality between a di-*tert*-butylsilylene ether and several common protective groups. Acetate and benzoate esters are highly compatible with the deprotection conditions (entries b–e), and no diminution of regioselectivity at the silylene ether (i.e., **12** vs **13**) was observed,[13] as might have occurred if complicated by neighboring group participation of the ester functionality. An allyl group easily survived the reaction conditions, as did benzyl, but the reaction with **11g** failed to go to completion. With **11h** selectivity between the methyl and silylene ethers was poor (entry h). The bulky triisopropylsilyl ether was unaffected during the deprotection with BF_3·SMe_2, whereas cleavage of the *tert*-butyl dimethylsilyl ether demarcates silicon reactivity (entries i and j).

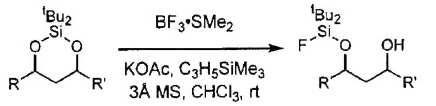
To ascertain whether deprotection could succeed selectively when challenged with substrates presenting less steric differentiation, silylene ethers derived from two secondary alcohols were examined (Table 2). In entries 1 and 2 a methyl and *tert*-butyl group were compared, and each reaction provided exclusively one isomeric fluorosilane.[13] The syn diastereomer (entry 2) required nearly three times as long (2.5 h) for complete consumption of starting material than did the anti diastereomer, and a third of the starting material was fully desilylated. Stopping the reaction in entry 2 prematurely before significant amounts of diol formed increased the yield to 79%, based on recovered starting material. Analogous results occurred with the anti and syn substrates shown in entries 3 and 4. Again, reaction with the syn diastereomer (entry 4) gave nearly 30% of unwanted diol when allowed to proceed until complete consumption of starting

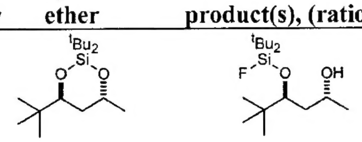
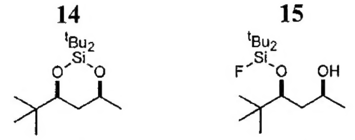
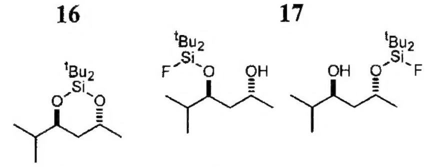
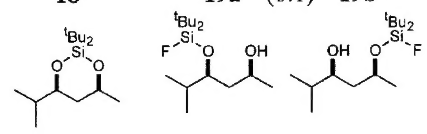
(12) The exact role of the KOAc is unclear, and related salts that proved less effective include NaOAc, CsOAc, *n*-$C_{15}H_{31}CO_2K$, $PhCO_2$Na, $PhCO_2K$, Na_2CO_3, K_2CO_3. Sodium 2-ethylhexanoate performed similarly to KOAc.

(13) Regiochemistry was determined by oxidation to the ketone/aldehyde or conversion of the alcohol to the iodide, cf., **8** and **9**. See Supporting Information.

(14) Trost, B. M.; Caldwell, C. G. *Tetrahedron Lett.* **1981**, *22*, 4999–5002.

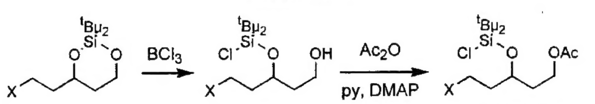
Table 2. Deprotection of Di-*tert*-butylsilylene Ethers Prepared from 2,4-Hexanediols



entry	silylene ether	product(s), (ratio)[a]	Yield[b]
1	 14	15	93%
2	 16	17	64%[c]
3	 18	19a (6:1) 19b	89%
4	 20	21a (6:1) 21b	43%

[a] Ratio determined by ^{19}F NMR of crude reaction mixtures, see ref 13. [b] Isolated yields, averaged from two runs. [c] 79% yield based on recovered starting material.

Scheme 4

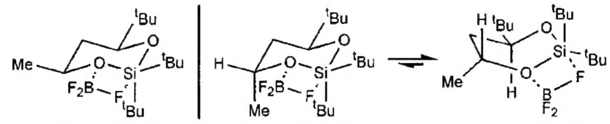


4, X = Ph
11i, X = OTIPS
22a, X = Ph
22b, X = OTIPS
23a, X = Ph, 81%
23b, X = OTIPS 80% (yield for 2 steps)

material. These experiments revealed that stereochemistry greatly influenced the efficiency of the desilylation reaction.

While cleavage of silyl ethers with BCl$_3$ is known,[8] it is interesting to note that selective mono-desilylation of the di-*tert*-butylsilylene ether **4** and **11i** occurred cleanly with BCl$_3$ (Scheme 4). However, the chlorosilanes had to be characterized as their acetates **23**, as the reactive free alcohols **22** reverted back to starting material (with up to 15% silanol formation) under acidic, neutral or basic conditions, including simply standing in CDCl$_3$ or methanol. The instability displayed by the chlorosilanes discouraged further investigation at this stage.

The regiochemistry observed in these selective deprotections was consistent with coordination of the boron to the more sterically accessible oxygen prior to delivery of fluoride.[15] For the syn diastereomers coordination by boron to the sterically more accessible α (equatorial) lone pair of the oxygen (**24**, Figure 1) might be expected as a



24, syn (chair) **25**, anti (chair) **26**, anti (boat)

Figure 1. Low energy reactive conformations.

key reaction intermediate. In an idealized chair conformation the equatorial oxygen lone pair would be antiperiplanar to the σ_{Si-O} bond of the other oxygen while positioning fluoride sufficiently close to donate electron density into an available orbital on silicon.[16] For the anti diastereomer in a chair conformation unfavorable 1,3-diaxial interactions exist between the axial methyl and a *tert*-butyl group on silicon, and molecular models suggested a boat (**26**) for the lower energy conformation where both the ring methyl and *tert*-butyl groups occupy quasi-equatorial positions.[17] In the boat conformation **26**, the boron can coordinate to the β or quasi-equatorial lone pair without severe steric crowding. The higher temperatures necessary for the deprotection of **1** (85 °C) along with the results in Table 2 suggest that conformational freedom to permit favorable orbital alignment may be key to efficient deprotection.

The initial difficulties encountered during the deprotection of **4** (Scheme 2) indicate the delicate balance between the rate of the mono-deprotection and the rate of the second desilylation leading to diol **3**. We speculate that the transition state corresponding to conformation **24** is higher in energy than for the anti diastereomer (**26**). The longer reaction times necessary for consumption of the syn diastereomers **16** and **20** allows the second desilylation event to become competitive in these reactions.

In conclusion, parameters influencing the regioselective mono-desilylation of di-*tert*-butylsilylene ethers using BF$_3$•SMe$_2$ have been elucidated. The reaction can be efficient, highly selective and provide access to 1,3-diols silylated at the sterically more hindered position. This new method is likely to see continued use in total synthesis.

Experimental Section

All reactions were run under an atmosphere of argon unless otherwise indicated. Reaction vessels were oven or flamed-dried and allowed to cool in a drybox or desiccator prior to use. Solvents and reagents were purified by standard methods.[18] CHCl$_3$ was purified by distillation from CaH$_2$ and stored

(15) Denmark, S. E.; Willson, T. M.; Almstead, N. G. *J. Am. Chem. Soc.* **1989**, *111*, 9258–9260.

(16) For a discussion of the precise orbitals that might be involved in this process the reader is referred to reviews on extracoordinate silicon chemistry: Brook, M. A. *Silicon in Organic, Organometallic, and Polymer Chemistry*; Wiley: New York, 2000, Chapter 2 and Chapter 5. Nucleophilic displacement at silanes with endocyclic leaving groups often occurs with retention. See: Bassindale, A. R.; Taylor, P. G. Reaction Mechanisms of Nucleophilic Attack at Silicon. In *The Chemistry of Organosilicon Compounds*; Patai, S.; Rappoport, Z.; Eds., Wiley: Chichester, UK, 1989; Vol. 1, Chapter 14. (b) Bassindale, A. R.; Taylor, P. G. Reaction Mechanisms of Nucleophilic Attack at Silicon. In *The Chemistry of Organosilicon Compounds*; Patai, S.; Rappoport, Z.; Eds., Wiley: Chichester, UK, 1988; Vol. 2, Chapter 9.

(17) Molecular modeling with Spartan software predicted that the ground state conformation for both the syn and anti diastereomers is best described as a half chair given the small dihedral angles for the C_{Me}–O–Si–O bond in the syn (+9°, chair) and anti (−10°, boat) diastereomers.

(18) Armarego, W. L. F.; Perrin, D. D. *Purification of Laboratory Chemicals*, 4th ed.; Oxford: Butterworth Heinemann, 1996.

over Na_2CO_3 under an Ar atmosphere in the dark. $BF_3{\cdot}SMe_2$ (Alfa-Aesar) and BCl_3 in heptane (Aldrich) were used as received from commercial sources. Powdered KOAc was flame dried as a melt under vacuum (0.1 mmHg). Thin-layer chromatography (TLC) was performed on EM 250 Kieselgel 60 F254 silica gel plates. The plates were visualized by staining with I_2 on silica, CAM,[19] ninhydrin, or potassium permanganate. Column chromatography was performed with silica gel 60 according to the method of Still.[20]

2,2-Di-*tert*-butyl-4-phenethyl-[1,3,2]-dioxasilinane (4). To a solution of diol **3**[21] (2.59 g, 14.4 mmol) in THF:Me_2NCHO (2:1, 30 mL) cooled to −30 °C was added $^tBu_2Si(OTf)_2$ (5.80 mL, 15.8 mmol) dropwise over 15 min. After 25 min the reaction mixture was neutralized with pyridine (2.40 mL, 30.0 mmol), allowed to warm to room temperature, and diluted with Et_2O (150 mL). The reaction mixture was washed with saturated $NaHCO_3$ solution, H_2O, and brine, dried ($MgSO_4$), and filtered through Celite. Volatiles were removed under reduced pressure, and the residue was purified by flash chromatography on silica gel using 20:1 hexanes−EtOAc for elution to provide the title compound as a colorless oil (4.01 g, 87%). R_f 0.70 (5% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35−7.20 (m, 5H), 4.12−4.02 (m, 3H), 2.90−2.71 (m, 2H), 1.93−1.73 (m, 3H), 1.62 (dd, J = 14.1, 1.5 Hz, 1H), 1.08 (d, J = 1.2 Hz, 9H), 1.06 (d, J = 1.2 Hz, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.7, 128.8, 128.5, 125.9, 73.0, 64.5, 40.7, 36.8, 31.6, 27.7, 27.4, 22.9, 20.1; HRMS *m/z* calcd for $C_{19}H_{32}O_2Si$ [M + H]$^+$ 321.1150, found: 321.2248.

3-(Di-*tert*-butyl-fluoro-silanyloxy)-5-phenyl-pentan-1-ol (5a). To a 10-mL round-bottomed flask containing **4** (350 mg, 1.09 mmol) were added KOAc (300 mg, 3.0 mmol) and freshly activated molecular sieves (3 Å, 250 mg). The flask was sealed with a rubber septum, flushed with argon, and treated sequentially with $CHCl_3$ (2.5 mL), allyl trimethylsilane (35 μL, 0.20 mmol), and $BF_3{\cdot}Me_2S$ (860 μL, 8.2 mmol, 7.5 equiv). After 5.5 h the mono-deprotection was complete (TLC), and the reaction mixture was transferred into a vigorously stirred saturated $NaHCO_3$ solution (10 mL) with the aid of CH_2Cl_2. The heterogeneous solution was filtered through a glass frit, and the organic layer was separated and washed with H_2O, brine, and dried ($MgSO_4$). After filtration through a small pad of Celite, volatiles were removed under reduced pressure. Purification of the residual oil by flash chromatography on silica gel with 15:1 hexanes−EtOAc for elution afforded the title compound as a colorless oil (301 mg, 81%). R_f 0.61 (33% EtOAc/hexanes); IR (thin film) ν 3450 (br) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36−7.21 (m, 5H), 4.42−4.38 (dddd, J = 5.3, 5.3, 5.3, 5.3 Hz, 1H), 3.92−3.79 (m, 2H), 2.77−2.72 (m, 2H), 2.36 (br s, 1H), 2.10−1.84 (m, 5H), 1.13 (s, 9H), 1.12 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.4 (C), 128.7 (CH), 128.6 (CH), 126.1 (CH), 72.0 (CH), 59.7 (CH_2), 39.1 (CH_2), 38.9 (CH_2), 31.5 (CH_2), 27.4 (CH_3), 20.7 (d, J = 15.1 Hz, C), 20.4 (d, J = 15.1 Hz, C); ^{19}F NMR (300 MHz, $CDCl_3$) δ −158.7; HRMS *m/z* calcd for $C_{19}H_{33}FO_2Si$ [M + H]$^+$ 341.2312, found: 341.2323.

3-(Di-*tert*-butyl-fluoro-silanyloxy)-5-phenylpentanoic Acid (7). To a room temperature solution of **5a** (150 mg, 0.44 mmol) in acetone (3.5 mL) was added Jones reagent[22] dropwise until a brown color persisted. The resulting solution was then treated with 2-propanol dropwise until the solution became green-blue. To the reaction mixture was added H_2O, and the organic solvent was removed under reduced pressure. The residue was redissolved in Et_2O, and the solution was washed with saturated $NaHCO_3$ solution, H_2O, and brine and dried ($MgSO_4$). The solution was filtered through Celite, and volatiles were removed under reduced pressure. Purification of the residual oil by flash chromatography on silica gel with 15:1 hexanes−EtOAc for elution provided the title compound as a yellow oil (112 mg, 72%). R_f 0.34 (50% EtOAc/hexanes); IR (thin film) ν 3110 (br), 1738 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33−7.19 (m, 5H), 4.61 (dddd, J = 5.9, 5.9, 5.9, 5.9 Hz, 1H), 2.78−2.63 (m, 4H), 2.03−1.95 (m, 2H), 1.07 (s, 18H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.1, 141.9, 128.7, 128.6, 126.2, 70.7, 42.1, 39.1, 31.3, 27.25, 27.21, 20.5 (d, J = 15.3 Hz), 20.4 (d, J = 15.3 Hz); ^{19}F NMR (300 MHz, $CDCl_3$) δ −158.8; HRMS *m/z* calcd for $C_{19}H_{31}FO_3Si$ [M + H]$^+$ 355.2105, found: 355.2100.

3-(Di-*tert*-butyl-fluoro-silanyloxy)-5-phenylpentanal (8). To a room temperature suspension of pyridinium chlorochromate (133 mg, 0.62 mmol) in CH_2Cl_2 (3.5 mL) was added a solution of **5a** (60 mg, 0.18 mmol) in CH_2Cl_2 (1.2 mL). After 2.5 h florisil and Et_2O (5 mL) were added to the reaction mixture, which was subsequently filtered through florisil. The volatile components were removed under reduced pressure and purification of the residue by flash chromatography on silica gel (20:1 hexanes−EtOAc for elution) provided the title compound as a colorless oil (109 mg, 82%). R_f 0.65 (25% EtOAc/hexanes); IR (thin film) ν 1722 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.88 (dd, J = 2.3, 2.3 Hz, 1H), 7.34−7.20 (m, 5H), 4.66 (dddd, J = 5.8, 5.8, 5.8, 5.8 Hz, 1H), 2.78−2.69 (m, 4H), 2.00 (ddd, J = 5.8, 2.9, 2.9 Hz, 2H), 1.07 (s, 18H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.5, 141.7, 128.7, 128.6, 126.3, 69.6, 50.7, 39.4, 31.5, 27.2, 20.6, 20.4; ^{19}F NMR (300 MHz, $CDCl_3$) δ −159.1; HRMS *m/z* calcd for $C_{19}H_3F_1O_2Si$ [M + H]$^+$ 339.2156, found: 339.2158.

Di-*tert*-butyl-fluoro-(3-iodo-1-phenethyl-propoxy)silane (9). To a room temperature solution of **5a** (160 mg, 0.47 mmol) and *p*-toluenesulfonyl chloride (106 mg, 0.59 mmol) in CH_2Cl_2 (4.5 mL) was added pyridine (0.5 mL, 6.2 mmol) in one portion. The resulting solution was stirred at room temperature for 20 h, and then volatiles were removed under reduced pressure. The resulting residue was dissolved in CH_2Cl_2, and the solution was washed with saturated $NaHCO_3$ solution, H_2O, and brine and dried ($MgSO_4$). After filtration through a pad of Celite, volatiles were removed under reduced pressure, and the residue was dissolved in a mixture of acetone (4.5 mL) and NaI (720 mg, 4.8 mmol, 10.0 equiv). After 30 h at reflux, the cooled reaction mixture was treated with saturated $NaHCO_3$ solution, and the acetone was removed under reduced pressure. The resulting mixture was extracted with EtOAc, and the combined organic layers were washed with H_2O and brine and dried ($MgSO_4$). After filtration through a pad of Celite, volatiles were removed under reduced pressure. Purification of the residual oil by flash chromatography on silica gel with 15:1 hexanes−EtOAc for elution provided the title compound as a pale yellow syrup (180 mg, 85%). R_f 0.57 (15% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34−7.19 (m, 5H), 4.23 (dddd, J = 6.5, 6.5, 6.5, 6.5 Hz, 1H), 3.30 (t, J = 7.2 Hz, 2H), 2.74−2.68 (m, 2H), 2.17 (ddd, J = 7.2, 7.2, 7.2 Hz, 2H), 1.96−1.89 (m, 2H), 1.08 (s, 18H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.1 (C), 128.7 (CH), 128.6 (CH), 126.1 (CH), 74.0 (CH), 41.0 (CH_2), 38.5 (CH_2), 31.3 (CH_2), 27.4 (CH_3), 27.3 (CH_3), 20.6 (C), 20.4 (C), 1.9 (CH_2); ^{19}F NMR (300 MHz, $CDCl_3$) δ −157.9; HRMS *m/z* calcd for $C_{19}H_{32}FIOSi$ [M + H]$^+$ 451.1330, found: 451.1334.

Acetic Acid 2,2-Di-*tert*-butyl-[1,3,2]dioxasilinan-4-ylmethyl Ester (11b). To a solution of (2,2-di-*tert*-butyl-[1,3,2]-dioxasilinan-4-yl)methanol[23] (2.52 g, 10.2 mmol) in CH_2Cl_2 (22 mL) was added pyridine (2.41 mL, 29.7 mmol) and Ac_2O (4.33 mL, 45.9 mmol). After 15 h at room temperature, the mixture was poured into a vigorously stirred saturated $NaHCO_3$ solution (20 mL). The organic layer was separated and washed with saturated NH_4Cl solution, H_2O, and brine, dried ($MgSO_4$), and filtered through Celite. Volatile components were removed under reduced pressure, and the residual oil was purified by flash chromatography on silica gel using 15:1 hexanes−EtOAc for elution to provide the title compound as a pale yellow oil (2.70 g, 92%). R_f 0.35 (15% EtOAc/hexanes); IR (thin film) ν 1744 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.31−4.27 (m, 1H), 4.13−4.08 (m, 3H), 4.03 (ddd, J = 11.0, 5.2, 1.0 Hz, 1H), 2.06

(19) See footnote 50 in: Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765−5780.

(20) Still, W. C.; Kahn, M.; Mitra, A. A. *J. Org. Chem.* **1978**, *43*, 2923−2925.

(21) Kiyooka, S.; Kaneko, Y.; Komura, M.; Matsuo, H.; Nakano, M. *J. Org. Chem.* **1991**, *56*, 2276−2278.

(22) Bowden, K.; Halsall, T. G.; Jones, E. R. H.; Weedon, B. C. L. *J. Chem. Soc.* **1946**, 39−45.

(23) See Supporting Information.

(s, 3H), 1.95−1.81 (m, 1H), 1.66 (ddd, J = 14.1, 4.1, 1.5 Hz, 1H), 1.01 (s, 9H), 0.98 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.1, 71.9, 68.4, 63.9, 33.1, 27.5, 27.2, 22.8, 21.1, 20.1; HRMS m/z calcd for $C_{14}H_{28}O_4Si$ [M + H]$^+$ 289.1835, found: 289.1833.

Benzoic Acid 2,2-Di-*tert*-butyl-[1,3,2]dioxasilinan-4-ylmethyl Ester (11d). To a solution of(2,2-di-*tert*-butyl-[1,3,2]-dioxasilinan-4-yl)methanol[23] (1.76 g, 7.2 mmol) in CH_2Cl_2 (20 mL) was added pyridine (1.00 mL, 12.3 mmol) and benzoyl chloride (2.51 mL, 21.6 mmol). After stirring for 13 h at room temperature the mixture was worked up as described for **11b**. Purification of the residual oil by flash chromatography on silica gel using 18:1 hexanes−EtOAc for elution provided the title compound as a colorless oil (2.23 g, 89%). R_f 0.45 (20% EtOAc/hexanes); IR (thin film) ν 1720 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.10−8.06 (m, 2H), 7.62−7.58 (m, 1H), 7.57−7.44 (m, 2H), 4.49−4.38 (m, 2H), 4.33−4.26 (m, 1H), 4.18 (ddd, J = 7.8, 2.5, 2.5 Hz, 2H), 2.06−1.94 (m, 1H), 1.79 (ddd, J = 13.8, 2.5, 2.5 Hz, 1H), 1.06 (s, 9H), 1.03 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.6, 133.2, 130.4, 129.8, 128.6, 72.0, 68.8, 64.0, 33.2, 27.6, 27.2, 22.9, 20.1; HRMS m/z calcd for $C_{19}H_{30}O_4Si$ [M + H]$^+$ 351.1992, found: 351.1985.

4-(2-Allyloxy-ethyl-2,2-di-*tert*-butyl-[1,3,2]-dioxasilinane (11f). To a room temperature solution of **11a** (1.22 g, 4.7 mmol) in CH_2Cl_2 (1.4 mL) and cyclohexane (2.8 mL) was added allyl trichloroacetimidate[24] (1.78 g, 8.9 mmol) and catalytic trifluoromethanesulfonic acid (~50 μL). After 3 h the reaction mixture was filtered through florisil and concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2, washed with saturated $NaHCO_3$ solution, H_2O, and brine and dried ($MgSO_4$). After filtration through Celite, the volatile components were removed under reduced pressure, and the residual oil was purified by flash chromatography on silica gel using 40:1 hexanes−EtOAc for elution to provide the title compound as a colorless oil (1.14 g, 81%). R_f 0.68 (20% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.98−5.81 (m, 1H), 5.30−5.14 (m, 2H), 4.27−4.19 (m, 1H), 4.10−4.07 (m, 2H), 3.99−3.96 (m, 2H), 3.66−3.52 (m, 2H), 1.88−1.66 (m, 3H), 1.60 (dddd, J = 14.1, 2.6, 2.6, 2.6 Hz, 1H), 1.02 (s, 9H), 0.98 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.2, 117.0, 72.2, 71.1, 66.6, 64.6, 38.9, 36.9, 27.7, 27.3, 22.9, 20.0; HRMS m/z calcd for $C_{16}H_{32}O_3Si$ [M + H]$^+$ 301. 2199, found: 301.2201.

2,2-Di-*tert*-butyl-4-(2-triisopropylsilanyloxy-ethyl)-[1,3,2]-dioxasilinane (11i). To a room temperature solution of **11a** (1.97 g, 7.6 mmol) in CH_2Cl_2 (7.5 mL) were added pyridine (1.22 mL, 15.0 mmol) and triisopropylsilyl chloride (1.58 mL, 11.4 mmol). The reaction mixture was stirred at room temperature for 20 h and then poured into a vigorously stirred saturated NH_4Cl solution (8 mL). The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with H_2O and brine and dried ($MgSO_4$). After filtration through Celite, volatiles were removed under reduced pressure. Purification of the residual oil by flash chromatography on silica gel using 30:1 hexanes−EtOAc for elution provided the title compound as a colorless oil (1.91 g, 90%). R_f 0.69 (5% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.29 (dddd, J = 12.8, 6.2, 6.2, 2.6 Hz, 1H), 4.13−4.08 (m, 2H), 3.95−3.79 (m, 2H), 1.91−1.77 (m, 1H), 1.73−1.61 (m, 3H), 1.11−0.98 (m, 39H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 70.9, 64.4, 59.7, 42.1, 37.0, 27.6, 27.4, 22.8, 20.0, 18.3, 12.2; HRMS m/z calcd for $C_{22}H_{48}O_3Si$ [M + H]$^+$ 417.3220, found: 417.3220.

Acetic Acid 2-(Di-*tert*-butyl-fluoro-silanyloxy)-4-hydroxy-butyl Ester (13b). The title compound was prepared from **11b** according to the general procedure described for the preparation of **5a**, except that 2.3 equiv of $BF_3{\cdot}Me_2S$ was used (colorless oil, 378 mg, 91%). R_f 0.48 (33% EtOAc/hexanes); IR (thin film) ν 3450 (br), 1744 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.42 (dddd, J = 4.2, 4.2, 4.2, 4.2 Hz, 1H), 4.09 (dddd, J = 11.2, 11.2, 11.2, 4.2 Hz, 2H), 3.94−3.71 (m, 2H), 2.39 (br s, 1H), 2.04 (s, 3H), 1.78 (ddd, J = 11.2, 3.8, 3.8 Hz, 2H), 1.01 (s, 9H), 1.00 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.3, 68.7, 68.0, 58.8, 37.0, 27.2, 27.1, 21.0, 20.5, 20.3; ^{19}F NMR (300 MHz, $CDCl_3$) δ −160.0; HRMS m/z calcd for $C_{14}H_{29}FO_4Si$ [M + H]$^+$ 309.1897, found: 309.1894.

Acetic Acid 3-(Di-*tert*-butyl-fluoro-silanyloxy)-5-hydroxy-pentyl Ester (13c). The title compound was prepared from **11c** according to the general procedure described for the preparation **5a**, except that 4.5 equiv of $BF_3{\cdot}Me_2S$ was used (colorless oil, 364 mg, 87%). R_f 0.55 (25% EtOAc/hexanes); IR (thin film) ν 3450 (br), 1743 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.38 (dddd, J = 6.0, 6.0, 6.0, 6.0 Hz, 1H), 4.15 (t, J = 6.5 Hz, 2H), 3.78−3.74 (m, 2H), 2.01 (s, 3H), 2.00−1.73 (m, 5H), 1.01 (d, J = 0.8 Hz, 9H), 1.00 (d, J = 0.8 Hz, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.3, 69.4, 61.2, 59.4, 39.3, 36.0, 27.3, 27.2, 21.2, 20.5 (d, J = 14.7 Hz), 20.4 (d, J = 14.7 Hz); ^{19}F NMR (300 MHz, $CDCl_3$) −159.1; HRMS m/z calcd for $C_{15}H_{31}FO_4Si$ [M + H]$^+$ 323.2054, found: 323.2054.

Benzoic Acid 2-(Di-*tert*-butyl-fluoro-silanyloxy)-4-hydroxy-butyl Ester (13d). The title compound was prepared from **11d** according to the general procedure described for the preparation of **5a**, except that 4.0 equiv of $BF_3{\cdot}Me_2S$ was used (colorless oil, 274 mg, 90%). R_f 0.69 (20% EtOAc/hexanes); IR (thin film) ν 3460 (br), 1720 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.04 (d, J = 7.3 Hz, 2H), 7.53−7.50 (m, 1H), 7.41 (dd, J = 7.3, 7.3 Hz, 2H), 4.57 (dddd, J = 5.5, 5.5, 5.5, 5.5 Hz, 1H), 4.37 (d, J = 4.8 Hz, 2H), 3.86−3.78 (m, 2H), 1.99−1.81 (m, 3H), 1.03 (s, 9H), 1.01 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.7, 133.3, 130.2, 129.9, 128.6, 70.0, 68.4, 59.2, 37.2, 27.2, 27.1, 20.5 (d, J = 14.0 Hz), 20.3 (d, J = 14.0 Hz); ^{19}F NMR (300 MHz, $CDCl_3$) δ −160.0; HRMS m/z calcd for $C_{19}H_{31}FO_4Si$ [M + H]$^+$ 371.2054, found: 371.2049.

Benzoic Acid 3-(Di-*tert*-butyl-fluoro-silanyloxy)-5-hydroxy-pentyl Ester (13e). The title compound was prepared from **11e** according to the general procedure described for the preparation of **5a**, except that 5.0 equiv of $BF_3{\cdot}Me_2S$ was used (colorless oil, 198 mg, 82%). R_f 0.67 (15% EtOAc/hexanes); IR (thin film) ν 3420 (br), 1720 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.04 (d, J = 7.5 Hz, 2H), 7.61−7.57 (m, 1H), 7.46 (dd, J = 7.5, 7.5 Hz, 2H), 4.48−4.42 (m, 3H), 3.91−3.77 (ddd, J = 7.6, 6.4, 6.4 Hz, 2H), 2.11 (ddd, J = 6.4, 6.4, 6.4 Hz, 2H), 1.97−1.84 (m, 3H), 1.82 (br s, 1H), 1.08 (s, 9H), 1.07 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.8, 133.2, 130.5, 129.8, 128.6, 69.6, 61.7, 59.5, 39.3, 36.1, 27.6, 27.3, 20.5 (d, J = 15.2 Hz), 20.4 (d, J = 15.2 Hz); ^{19}F NMR (300 MHz, $CDCl_3$) δ −159.1; HRMS m/z calcd for $C_{20}H_{33}FO_4Si$ [M + H]$^+$ 385.2210, found: 385.2210.

5-Allyloxy-3-(di-*tert*-butyl-fluoro-silanyloxy)pentan-1-ol (13f). The title compound was prepared from **11f** according to the general procedure described for the preparation of **5a**, except that 6.5 equiv of $BF_3{\cdot}Me_2S$ was used (colorless oil, 219 mg, 78%). R_f 0.59 (20% EtOAc/hexanes); IR (thin film) ν 3395 (br) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.98−5.85 (m, 1H), 5.31−5.16 (m, 2H), 4.44 (dddd, J = 5.8, 5.8, 5.8, 5.8 Hz, 1H), 3.97 (ddd, J = 5.5, 3.1, 1.6 Hz, 2H), 3.94−3.74 (m, 2H), 3.58−3.52 (m, 2H), 2.15 (br s, 1H), 1.96−1.77 (m, 4H), 1.07 (d, J = 0.9 Hz, 9H), 1.06 (d, J = 0.9 Hz, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.0, 117.2, 72.2, 70.3, 66.7, 59.7, 39.3, 37.0, 27.3, 27.2, 20.5 (d, J = 12.1 Hz), 20.3 (d, J = 12.1 Hz); ^{19}F NMR (300 MHz, $CDCl_3$) δ −159.3; HRMS m/z calcd for $C_{16}H_{33}FO_3Si$ [M + H]$^+$ 321.2261, found: 321.2252.

5-Benzyloxy 3-(di-*tert*-butyl-fluoro-silanyloxy)pentan-1-ol (13g). The title compound was prepared from **11g** according to the general procedure described for the preparation of **5a**, except that 6.5 equiv of $BF_3{\cdot}Me_2S$ was used (colorless oil, 65 mg, 35%). R_f 0.62 (15% EtOAc/hexanes); IR (thin film) ν 3405 (br) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39−7.28 (m, 5H), 4.60−4.45 (m, 3H), 3.84−3.77 (m, 2H), 3.61 (dd, J = 6.2, 6.2 Hz, 2H), 2.00−1.84 (m, 4H), 1.69 (br s, 1H), 1.07 (d, J = 0.8 Hz, 9H), 1.05 (d, J = 0.8 Hz, 9H); ^{19}F NMR (300 MHz, $CDCl_3$) δ −159.3; HRMS m/z calcd for $C_{20}H_{35}FO_3Si$ [M + H]$^+$ 371.2418, found: 371.2419.

3-(Di-*tert*-butyl-fluoro-silanyloxy)-5-methoxy-pentan-1-ol (13h). The title compound was prepared from **11h** according to the general procedure described for the preparation of **5a**, except that 3.5 equiv of $BF_3{\cdot}Me_2S$ was used (colorless oil, 31 mg, 43%). R_f 0.32 (33% EtOAc/hexanes); IR (thin film) ν 3390 (br) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.43

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(dddd, J = 6.1, 6.1, 6.1, 6.1 Hz, 1H), 3.85–3.72 (m, 2H), 3.53–3.45 (m, 2H), 3.35 (s, 3H), 2.04 (br s, 1H), 1.97–1.79 (m, 4H), 1.07 (s, 9H), 1.06 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 70.3, 69.1, 59.7, 58.8, 39.3, 37.0, 27.3, 27.2, 20.6 (d, J = 15.1 Hz), 20.5 (d, J = 15.1 Hz); ^{19}F NMR (300 MHz, $CDCl_3$) δ −159.4; HRMS *m/z* calcd for $C_{20}H_{36}FO_3Si$ [M + H]$^+$ 371.2418, found: 371.2419.

3-(Di-*tert*-butyl-fluoro-silanyloxy)-5-triisopropylsilanyloxy-pentyl-1-ol (13i). The title compound was prepared from **11i** according to the general procedure described for the preparation of **5a**, except that 7.0 equiv of $BF_3{\cdot}Me_2S$ was used (colorless oil, 170 mg, 78%). R_f 0.48 (15% EtOAc/hexanes); IR (thin film) ν 3380 (br) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.48 (dddd, J = 5.9, 5.9, 5.9, 5.9 Hz. 1H), 3.88–3.76 (m, 3H), 2.03–1.91 (m, 2H), 1.89–1.77 (m, 1H), 1.63 (br s, 1H), 1.09–1.06 (m, 39H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 70.6, 60.1, 59.9, 40.1, 39.0, 27.3, 20.6 (d, J = 12.0 Hz), 20.3 (d, J = 12.0 Hz), 18.2, 12.2; ^{19}F NMR (300 MHz, $CDCl_3$) δ −159.4; HRMS *m/z* calcd for $C_{22}H_{49}FO_3Si_2$ [M + H]$^+$ 437.3283, found: 437.3282.

4-(Di-*tert*-butyl-fluoro-silanyloxy)-5,5-dimethyl-hexan-2-ol (15). The title compound was prepared from **14** according to the general procedure described for the preparation of **5a**, except that 3.0 equiv of $BF_3{\cdot}Me_2S$ were used (colorless oil, 255 mg, 93%). R_f 0.44 (33% EtOAc/hexanes): IR (thin film) ν 3415 (br) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.12 (qdd, J = 6.2, 12.2, 2.3 Hz, 1H), 4.02 (dd, J = 8.3, 1.8 Hz, 1H), 1.64–1.55 (m, 1H), 1.51 (br s, 1H), 1.45 (ddd, J = 14.6, 8.3, 2.5 Hz, 1H), 1.27 (d, J = 6.2 Hz, 3H), 1.05 (s, 9H), 1.04 (s, 9H), 0.91 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 80.1, 64.6, 42.8, 35.8, 27.5, 27.3, 26.2, 24.9, 21.1 (d, J = 16.0 Hz), 20.3 (d, J = 16.0 Hz); ^{19}F NMR (300 MHz, $CDCl_3$) δ −152.0; HRMS *m/z* calcd for $C_{16}H_{35}FO_2Si$ [M + H]$^+$ 307.2469, found: 307.2453.

4-(Di-*tert*-butyl-fluoro-silanyloxy)-5,5-dimethyl-hexan-2-ol (17). The title compound was prepared from **16** according to the general procedure described for the preparation **5a**, except that 5.0 equiv of $BF_3{\cdot}Me_2S$ was used (colorless oil, 178 mg, 64%). R_f 0.42 (40% EtOAc/hexanes); IR (thin film) ν 3365 (br) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.00–3.91 (m, 1H), 3.80 (ddd, J = 6.1, 3.6, 1.5 Hz, 1H), 1.77 (ddd, J = 14.8, 6.9, 3.6 Hz, 1H), 1.64–1.55 (m, 3H), 1.17 (d, J = 6.1 Hz, 3H), 1.04 (d, J = 1.0 Hz, 9H), 1.03 (d, J = 1.0 Hz, 9H), 0.90 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 80.7, 66.7, 44.2, 36.2, 27.4, 27.1, 25.9, 23.6, 21.1 (d, J = 15.0 Hz), 21.0 (d, J = 15.0 Hz); ^{19}F NMR (300 MHz, $CDCl_3$) δ −153.2; HRMS *m/z* calcd for $C_{16}H_{35}FO_2Si$ [M + H]$^+$ 307.2469, found: 307.2461.

4-(Di-*tert*-butyl-fluoro-silanyloxy)-5-methyl-hexan-2-ol (19a) and 5-(Di-*tert*-butyl-fluoro-silanyloxy)-2-methyl-hexan-3-ol (19b). The title compounds were prepared from **18** according to the general procedure described for the preparation of **5a**, except that 2.5 equiv of $BF_3{\cdot}Me_2S$ was used. Purification of the reaction mixture by flash chromatography on silica gel using 10:1 hexanes–EtOAc for elution provided the title compounds **19a** and **19b** as colorless oils. **19a:** 138 mg, 76%; R_f 0.45 (33% EtOAc/ hexanes); IR (thin film) ν 3365 (br) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.13 (dddd, J = 4.1, 4.1, 4.1, 4.1 Hz, 1H), 4.06–3.99 (m, 1H), 2.05–2.00 (br s, 1H), 1.92 (dddd, J = 7.6, 4.1, 4.1, 0.4 Hz, 1H), 1.54–1.43 (m, 2H), 1.18 (d, J = 6.3 Hz, 3H), 1.01 (s, 18H), 0.87 (dd, J = 6.9, 6.9 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 75.9, 64.3, 41.2, 33.6, 27.2, 24.4, 20.5, 20.3, 18.1, 16.8; ^{19}F NMR (300 MHz, $CDCl_3$) δ −157.0; HRMS *m/z* calcd for $C_{15}H_{33}FO_2Si$ [M + H]$^+$: 293.2312, found: 293.2308. **19b:** 23 mg, 13%; R_f 0.34 (33% EtOAc/ hexanes); IR (thin film) ν 3350 (br) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.57–4.48 (m, 1H), 3.70 (ddd, J = 9.3, 8.1, 2.7 Hz, 1H), 2.51 (br s, 1H), 1.67–1.47 (m, 3H), 1.29 (d, J = 6.1 Hz, 3H), 1.03 (d, J = 1.1 Hz, 9H), 1.01 (d, J = 1.1 Hz, 9H), 0.89 (dd, J = 6.7, 6.7 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 72.7, 68.7, 41.7, 33.9, 27.0, 26.9, 23.3, 20.4 (d, J = 15.3 Hz), 19.8 (d, J = 15.3 Hz), 18.4, 17.6; ^{19}F NMR (300 MHz, $CDCl_3$) δ −162.0; HRMS *m/z* calcd for $C_{15}H_{33}FO_2Si$ [M + H]$^+$ 293.2312, found: 293.2319.

4-(Di-*tert*-butyl-fluoro-silanyloxy)-5-methyl-hexan-2-ol (21a). The title compound was prepared from **20** according to the general procedure described for the preparation of **5a**, except that 2.5 equiv of $BF_3{\cdot}Me_2S$ was used (colorless oil, 136 mg, 37%). R_f 0.48 (33% EtOAc/hexanes); IR (thin film) ν 3330 (br) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.16 (dddd, J = 4.2, 4.2, 4.2, 0.8 Hz, 1H), 3.92–3.86 (m, 1H), 2.39 (br s, 1H), 1.98 (qdd, J = 6.8, 6.8, 6.8 Hz, 1H), 1.68–1.47 (m, 3H), 1.18 (d, J = 6.1 Hz, 3H), 1.05 (d, J = 0.8 Hz, 9H), 1.03 (d, J = 0.8 Hz, 9H), 0.93 (d, J = 6.8 Hz, 3H), 0.84 (d, J = 6.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 79.1, 67.2, 40.5, 33.4, 27.5, 27.4, 24.1, 20.9, 18.1, 16.8; ^{19}F NMR (300 MHz, $CDCl_3$) δ −156.6; HRMS *m/z* calcd for $C_{15}H_{33}FO_2Si$ [M + H]$^+$ 293.2312, found: 293.2305.

Acetic Acid 3-(Di-*tert*-butyl-chloro-silanyloxy)-5-phenyl-pentyl Ester (23a). To a room temperature solution of **4** (540 mg, 1.69 mmol) in $CHCl_3$ (5.5 mL) was added BCl_3 (2.1 mL, 1.0 M in heptane, 2.1 mmol). After 25 min TLC analysis of an aliquot indicated the reaction was complete, and the reaction mixture was transferred with the aid of CH_2Cl_2 into a stirring saturated $NaHCO_3$ solution (8 mL). The organic layer was separated, washed with H_2O and brine, and dried ($MgSO_4$). After filtration through a small pad of Celite, volatiles were removed under reduced pressure and the residue was purified by flash chromatography on silica gel using 10:1 hexanes–EtOAc for elution to provide the alcohol **22a** as a colorless oil (534 mg, 89%). R_f 0.38 (33% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35–7.20 (m, 5H), 4.36 (dddd, J = 5.7, 5.7, 5.7, 5.7 Hz, 1H), 3.95–3.88 (m, 1H), 3.84–3.76 (m, 1H), 2.75–2.68 (m, 2 H), 2.05–1.85 (m, 4H), 1.75 (br s, 1H), 1.14 (s, 9H), 1.13 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.3, 128.7, 128.6, 126.1, 72.3, 59.5, 38.3, 38.2, 31.3, 27.6, 27.5, 23.5, 23.3. The oil was immediately acylated according to the general procedure described for the preparation of **11b** to afford the product as colorless oil (544 mg, 91%). R_f 0.67 (10% EtOAc/ hexanes); IR (thin film) ν1739 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35–7.18 (m, 5H), 4.32–4.20 (m, 3H), 2.72 (dddd, J = 13.5, 7.8, 2.7, 2.7 Hz, 2H), 2.08 (s, 3H), 2.03–1.99 (m, 4H), 1.12 (s, 18H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.3, 142.2, 128.7, 128.6, 126.1, 71.5, 61.3, 38.2, 34.7, 31.1, 27.6 23.4, 21.3; HRMS *m/z* calcd for $C_{21}H_{35}ClO_3Si$ [M + H]$^+$ 399.2122, found: 399.2115.

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Supporting Information Available: Preparation of starting materials (**11a**, **11c**, **11e**, **11g**, **11h**, **11j**, **14**, **16**, **18**, **20**), regiochemical proofs for **6a**, **13b**, **13c**, **13f**, **13i**, **15**, **19a**, characterization data for **5b**, **6a**, **6b**, **23b**, and copies of NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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